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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/781,891	02/02/2001	William Delaney IV	13381	8348

7590

05/29/2003

SCULLY, SCOTT, MURPHY & PRESSER
400 Garden City Plaza
Garden City, NY 11530

EXAMINER

GUZO, DAVID

ART UNIT

PAPER NUMBER

1636

DATE MAILED: 05/29/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/781,891

Applicant(s)

DELANEY ET AL.

Examiner

David Guzo

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 September 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15, 23 and 24 is/are rejected.
- 7) ☒ Claim(s) 16-22 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10/15/01 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6.
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice to Comply with Sequence Rules.

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Detailed Action

Abstract

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

In the present case, the Abstract is over 150 words.

Title

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "Method for Detection of Variant HBV".

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

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Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specifically, non-initialed changes have been made to the residence address of inventor Harriet Isom.

Improper Multiple Dependent Claims

Claims 16-22 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims 16-22 have not been further treated on the merits.

35 USC 112, 1st Paragraph Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 and 23-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed methods of detecting HBV variants or HBV DNA polymerase activity using HepG2 cells, does not reasonably provide enablement for the same methods using any cells or cell lines. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

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Applicants claim a method for detecting a variant HBV which exhibits an altered sensitivity to an agent and a method for detecting HBV DNA polymerase activity in the presence of an antiviral agent, wherein said methods use any cell infected with a baculovirus-HBV construct. Applicants have provided examples of the claimed method using the human liver tumor cell line HepG2.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Teletronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986 and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988)). These factors include the following:

1) Unpredictability of the art. The art in this case involves the use of baculoviral-HBV viruses to infect cells wherein said cells must be capable of being infected by baculoviruses, must be capable of supporting expression of heterologous nucleic acid sequences (replication competent HBV genomes) vectored into said cells by the baculoviruses, must be capable of supporting HBV replication, HBV gene (i.e. HBV DNA polymerase) expression, assembly of HBV particles and/or release of HBV particles. The prior art shows that use of recombinant baculoviruses to express genes or sequences of interest in mammalian cells is unpredictable. For example, Boyce et al. (PNAS, 1996, Vol. 93, pp. 2348-2352, see whole article, particularly Table 1) demonstrated that baculoviral vectors were not able to express statistically significant

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(or detectable above background) levels of a reporter gene in most mammalian cell lines infected with the baculoviral vectors. With regard to human liver cells, Boyce et al. shows an unpredictability as well, with the HepG2 cell line being particularly susceptible to baculoviral infection and reporter gene expression while another human liver cell line (Sk-Hep-1) showed no detectable expression of the reporter gene (i.e. level of the reporter gene was identical to the level in mock infected cells).

With regard to use of non-liver cells for infection by the instant baculoviral-HBV vectors, the prior art indicates that the target tissue for HBV infection is the liver. Whether other non-liver cell lines could support HBV replication, gene expression, etc. as well as be capable of being infected with recombinant baculoviruses in a meaningful manner for the purposes of the instant detection method is unclear.

2) State of the art. The state of the art with regard to infection of non-liver cell lines with recombinant baculoviral-HBV vectors is poorly developed. Only HepG2 cell lines have been successfully infected with recombinant baculoviral-HBV vectors.

3) Number of working examples. Applicants present working examples of the claimed invention using only HepG2 cells.

4) Amount of guidance provided by applicants. Applicants provide teachings only using HepG2 cells. Applicants indicate that other cells and cell lines can be used but present no guidance on how said cells can be constructed (what multiplicities of infection by baculoviral-HBV vectors are necessary, what levels of HBV expression can be achieved in other cells, whether the levels of HBV gene expression are significant enough to be usable in the claimed method, etc.).

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5) Nature of the invention. The invention involves a complex area of biotechnology; the use of recombinant baculoviral-HBV vectors in a detection method for identification of anti-HBV agents.

6) Level of skill in the art. The level of skill in the art is high; however, given the unpredictability of the art, the lack of working examples, the poorly developed state of the art and the lack of guidance presented by applicants, it must be considered that the skilled artisan would need to have conducted essentially trial and error experimentation to practice the entire scope of the claimed invention.

Given the above analysis of the factors which the courts have determined are essential for enablement of a claimed invention, it must be concluded that the skilled artisan would have needed to have conducted undue and excessive experimentation in order to practice the full scope of the claimed invention.

35 USC 112, 2nd Paragraph Rejections

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 and 23-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-15 and 23 (and dependent claims) are vague in that in Claim 1, line 14 and Claim 23, lines 10-11, applicants recite "the variant virus". This is unclear because the claims do not provide antecedent basis for the term "the variant virus". Also, the

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term "the variant virus" is unclear because there are two different variant viruses (HBVs) recited in the claims and it is unclear which variant virus is being referred to.

Claim 4 is vague in that applicants recite an agent which can be both a non-nucleoside analogue reverse transcriptase inhibitor **and** a non-nucleoside analogue DNA-dependent DNA polymerase inhibitor. It is unclear if any given agent can be **both** a non-nucleoside reverse transcriptase inhibitor **and** a non-nucleoside analogue DNA-dependent DNA polymerase inhibitor.

Claim 24 is vague in that the preamble of the claim is broader than what is supported in the rest of the claims. The preamble recites a method for detecting any DNA polymerase activity in the presence of an antiviral agent but the rest of the claim recites detecting only DNA polymerase produced by HBV. The method recites no step(s) whereby non-HBV DNA polymerase activity in the presence of an antiviral agent can be detected.

Claims 23 and 24 are vague in the recitation of the phrase "...non-nucleoside analogues (emphasis added) DNA dependent DNA polymerase inhibitors." because the term "analogues" in the context of the claim should be single rather than plural.

Redrafting the claims to recite "...nucleoside analogue DNA dependent DNA polymerase inhibitors." would be remedial.

Claim 24 is vague in the recitation of the phrase "...sufficient for the HBV and to replicate..." as this phrase makes no sense.

Claim 24 is also vague in the recitation of the phrase "...therefrom to HBV polymerase assay...". Insertion of the article "a" prior to "HBV" would be remedial.

Sequence Listing

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The **nucleotide sequence** presented on pages 33-34 is listed in the sequence listing as SEQ ID NO:7; however SEQ ID NO:7 is an **amino acid sequence**. Also, the amino acid sequence present in Fig. 3 is not identified by SEQ ID NO identifier.

Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Applicant is requested to return a copy of the attached Notice to Comply with the reply. Any reply to this Office Action which does not fully comply with the sequence rules will be considered non-responsive. The nature of the non-compliance with the sequence rules has however not precluded an examination of the application on the merits, the results of which are presented above.

The closest prior art is represented by Delaney et al. (Antimicrobial Agents and Chemotherapy, 1999, Vol. 43(8), pp. 2017-2026) and Delaney et al. (J. Hepatology, 1998, Vol. 28, pp. 1134-1146), both cited by applicants. While the prior art describes the use of recombinant baculoviral-HBV vectors to introduce HBV sequences into

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HepG2 cells and the potential use of these cells for testing antiviral compounds, the prior art does not teach the claimed methods for detection of variant HBVs (or HBV polymerases) which exhibit altered sensitivity to antiviral agents.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Faxes may be sent directly to the examiner at (703) 746-5061.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David Guzo
May 28, 2003

DAVID GUZO
PRIMARY EXAMINER
